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10/782,456	02/19/2004	Denisa D. Wagner	CFBF-P02-015	5162

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EXAMINER	
GAMBEL, PHILLIP	
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1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,456	WAGNER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 6, 9-22 and 52-57* is/are pending in the application.

4a) Of the above claim(s) *6,8,10,11,19-21 and 54-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,12,13,15-18,22 and 50-53* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's amendment, filed 04/05/2007, has been entered.

Claims 2-5, 7 and 23-50 have been canceled in this amendment or previously.

Claims 1, 9, 12, 16, 17, 52 and 54 have been amended.

Claims 1, 6, 9-22 and 52-57 are pending.

Applicant's election of Group I, drawn to methods of treating hemostasis and disorders with P-selectin and the species of "P-selectin activity increasing the levels of P-selectin in plasma and Hemophilia A in the Response to Restriction Requirement, filed 10/12/2006, has been acknowledged.

Claims 1, 9, 12-18, 22, 50-52 and 53 are under consideration as they read on the elected Group I, drawn to methods of treating hemostasis and disorders with P-selectin.

Upon a review of the claims, it appears that claim 51 should be included in the elected invention, rather than being withdrawn from consideration.

Claims 6, 8, 10, 11, 19-21 and 54-57 have been withdrawn from consideration as they read on non-elected Groups and species.

2. In view of applicant's amended claims, the previous rejections under 35 USC 112, first paragraph, have been withdrawn.

However, upon reconsideration and an updated search, the following New Grounds of Rejection have been set forth herein.

The examiner apologizes for any inconvenience to applicant in this matter.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 9, 12-13, 15-18, 22, 50-52 and 53 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

In evaluating the facts of the instant case, the following is noted:

Applicant has not disclosed how to use P-selectin or P-selectin fusion proteins to induce hemostasis in the treatment or prevention of any disorder associated with hypocoagulation or vasculature-associated disease in a subject as a therapeutic regimen for human diseases.

There is insufficient information or nexus with respect to using P-selectin or P-selectin fusion proteins to treat the disorders or diseases commensurate in scope with the claimed invention, particularly with the predictability of treating the claimed and intended human diseases.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.
See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as adhesion molecule modulators can be species- and model-dependent, it is not clear that reliance on the disclosed in vitro experimental results and the known in vivo animal studies accurately reflects the relative efficacy of the claimed therapeutic strategies to treat the scope of disorders associated with hypocoagulation or vasculature-associated diseases encompassed by the claimed invention.

For example, pages 6-7 of the instant specification provides the following.

The methods of the present invention are also useful for the treatment of a vasculature-associated disease. As used herein, a "vasculature-associated disease" is a disease having a pathology that is dependent on a vascular blood supply. Thus, it is contemplated that achieving coagulation in the vasculature of the disease site, e.g., in the intratumoral vasculature of a solid tumor, would prove beneficial. Such vasculature-associated diseases include benign and malignant tumors or growths, such as BPH, diabetic retinopathy, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, neovascular glaucoma and psoriasis. Also included within this group are synovitis, dermatitis, endometriosis, angiofibroma, rheumatoid arthritis, atherosclerotic plaques, corneal graft neovascularization, hemophilic joints, hypertrophic scars, osler-weber syndrome, pyogenic granuloma

retrolental fibroplasia, scleroderma, trachoma, and vascular adhesions.

In one embodiment, an inducer of P-selectin activity, e.g., soluble P-selectin, is administered in addition to therapies designed to induce thrombosis of tumor blood vessels, in order to potentiate tumor necrosis.

With respect to the unpredictability of treating diseases disclosed and targeted by the claimed methods, the following is noted.

Krause et al. (Clinical & Experimental Metastasis 17: 183-192, 1999) describes the following.

As tumor cell-induced activation of platelets is regarded as an important step in metastasis, it is speculated that an underlying mechanism in metastasis might be the stimulation of P-selectin expression on platelets.

It can be concluded that the specific site of P-selectin expression and the timing of this express are both important in affecting the metastasis of different tumor types. To evaluate the role of P-selectin in the interaction between platelets, tumor cells and endothelial cells is a very promising approach for metastasis research in the future, because it might provide further insights into the complex signaling pathways and mediators involved in tumor cell extravasation.

See entire document, particularly P-selectin on pages 188-189.

With respect to certain diseases such as diabetes and arthritis, which are encompassed by the claimed methods, as described in the instant specification,

Varki et al. (U.S. Patent No. 6,596,705) employs the inhibitor of P-selectin PSGL-1 to treat the very same or nearly the same "vasculature-associated diseases" that the instant methods are drawn to provide an agonist or inducer of hemostasis.

See entire document, including Table 1 on columns 6-10 of U.S. Patent No. 6,596,705.

Therefore, the scope of diseases and disorders targeted by the claimed methods encompass diseases and disorders that the skilled artisan has targeted with P-selectin antagonists and not with P-selectin itself, as claimed.

While the evidence of record indicates that the use of P-selectin or P-selectin fusioin protein for the treatment of an experimental model of hemophila,

there is insufficient information whether one could induce hemostasis and treat the disorders and conditions as broadly claimed,

particularly given the role of P-selectin in the very conditions encompassed by the claimed invention,

and given that the skilled artisan provided P-selectin antagonists to treat or to target the very same conditions as encompassed by the instant methods.

Therefore, the instant specification fails to provide sufficient enablement for the use of P-selectin, particularly its role as an inducer of hemostatis to treat the scope of diseases and disorders encompassed by the claimed methods.

There appears to be insufficient evidence that applicant's reliance on the use of P-selectin or P-selectin fusion protein in the treatment of experimental models of hemophilia would indicate that the claimed therapeutic modalities based upon inducing hemostasis would operate on either acute or chronic disorders or diseases, commensurate in scope with the claimed invention.

Although an adhesion molecule-receptor pair may be expressed and play a role in leukocyte accumulation in various inflammatory conditions, the ability of an adhesion molecule agonist (or antagonist) to affect some therapeutic endpoint will depend on the adhesion molecule agonist (or antagonist) and the nature of the disease (e.g. acute versus chronic, tissue specificity, etc.).

In humans, the diseases or disorders encompassed by the claimed methods are already established before therapy is offered.

Further, with respect to the recitation of "preventing a disorder", the following is noted.

The specification does not adequately teach how to effectively prevent any disorder associated with hypocoagulation in order to reach an appropriate beneficial therapeutic endpoint in humans by administering P-selectin or P-selectin fusion proteins. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations as well as clinical experience with P-selectin to the development of effective methods of preventing human disorders associated with hypocoagulatoin broadly encompassed by the claimed invention and consistent with the disclosure of various disorders (e.g., hemophilia) disclosed on page 9, paragraph 2 of the instant specification.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the agonist / antagonist and the stimulus / insult occur at the same or nearly the same time. Immunomodulation is much easier to achieve under such controlled conditions that experienced in the human disorders or diseases, such as the disorders targeted and broadly encompassed by the claimed invention (see page 9, paragraph 2 of the instant specification). With respect to in vivo studies, animal models validate concepts based on studies of human diseases, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Generally, such diseases are diagnosed only after significant tissue damage has occurred.

There is insufficient guidance and direction as well as objective evidence to provide for preventing the diversity and scope of disorders or diseases encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based (e.g., P-selectin) therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating or preventing hemostasis, disorders associated with hypocoagulation or vasculature-associated diseases, broadly encompassed by the claimed methods.

Applicant is invited to provide objective evidence to support the enablement of the scope disorders and diseases encompassed by the claimed methods.

Alternatively, applicant is invited to amend the claims to those disorders or diseases that are enabled, such as hemophilia.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. For examination purposes, P-selectin is known and has been known as GMP-140, PADGEM and CD62P.

8. Claims 1, 9, 12, 15-18 and 22 are rejected under 35 U.S.C. § 102(b) as anticipated McEver (U.S. Patent No. 5,378,464) (see entire document, including the Claims).

McEver teaches modulating hemostatic reactions and inflammatory conditions, including tumors (e.g., see column 20, paragraph 1; column 21, paragraph 5) as well as promoting and inhibiting the anticoagulant effects of protein S (e.g., see column 20, paragraph 4) with soluble GMP-140 (see entire document, including Diagnosis and Treatment of Disorders of the Inflammatory Response System on columns 20-23 and Claims).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.
See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

It is the burden of the applicant to show the unobvious difference between the claimed and disclosed methods and compositions. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Also, the Courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

9. Claims 1, 9, 12, 15-18, 22 and 51-53 are rejected under 35 U.S.C. § 103 as being unpatentable over Cochrum et al. (U.S. Patent No. 5,510,102) in view of McEver (U.S. Patent No. 5,378,464) and Larsen et al. (U.S. Patent No. 6,277,975).

Cochrum et al. teach the use of hemostatic adhesive agents for the treatment of various cardiovascular and vascular conditions (see entire document, including Utility on columns 10-11 and Claims).
Here on column 11, paragraph 2, Cochrum et al. teach that P-selectin plays an important role in hemostasis, inflammation and wound repair and, in turn, plays an important role in the advantages of platelets in adhesive agents in the referenced utilities.

Cochrum et al. differs from the claimed methods by not disclosing the use (rather than the role) of P-selectin in such adhesive agents in therapeutic modalities associated with hemostasis.

McEver teaches modulating hemostatic reactions and inflammatory conditions, including tumors (e.g., see column 20, paragraph 1; column 21, paragraph 5) as well as promoting and inhibiting the anticoagulant effects of protein S (e.g., see column 20, paragraph 4) with soluble GMP-140 (see entire document, including Diagnosis and Treatment of Disorders of the Inflammatory Response System on columns 20-23 and Claims).

McEver differs from the claimed methods by not teaching the well known use of fusion proteins or immunoglobulin fusion proteins in the administration of therapeutic molecules of interest, including adhesion molecules.

Immunoglobulin fusion proteins, including the use of human IgG1 were well known in the art in providing increased half-life and immunoglobulin Fc effector functions in therapeutic modalities at the time the invention was made, including the use of said fusion proteins with adhesion molecules.

For example, Larsen et al. teach the well known use of fusion proteins or immunoglobulin fusion proteins in the administration of therapeutic molecules of interest, including adhesion molecules (see entire document, including columns 10-11).

Given the role of P-selectin in hemostatic reactions as taught by Cochrum et al. and McEver, the ordinary artisan would have been motivated to add P-selectin to the adhesive compositions taught by Cochrum to employ in certain therapeutic modalities involved with hemostasis. Given the referenced role of P-selectin itself, the ordinary artisan would have been motivated to incorporate P-selectin into the adhesive compositions and treatments of Cochrum et al. to take advantage of the important role of P-selectin in hemostatic reactions. Note, too, that McEver teaches and claims the use of GMP-140 (i.e., P-selectin) in both the positive and negative regulation via P—selectin mediated interactions, as addressed above. Given the teachings of Cochrum et al. and McEver, it would have been obvious to the ordinary artisan to employ the P-selectin in the adhesive compositions and therapeutic modalties of Cochrum et al. to take advantage of the important hemostatic or procoagulant properties of P-selectin in the treatment of hemostasis, inflammation and wound repair. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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